

**BIOGRAPHICAL SKETCH**

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NAME: Boyer, Thomas G.

eRA COMMONS USER NAME: boyertg

POSITION TITLE: Professor of Molecular Medicine

**EDUCATION/TRAINING**

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Frostburg State University, Frostburg, MD	B.S.	05/1983	Biology
Frostburg State University, Frostburg, MD	B.S.	05/1983	Wildlife/Fisheries Mgmt
State University of New York at Buffalo, NY	Ph.D.	05/1990	Biochemistry
University of California, Los Angeles, CA	Postdoc	12/1998	Molecular Genetics

**A. PERSONAL STATEMENT**

The long-term goal of my laboratory is to understand how fundamental mechanisms of eukaryotic transcription control are subverted during developmental diseases and cancer, with an emphasis on women's reproductive cancers. This objective conforms well to my training and expertise in the field of RNA polymerase II (Pol II) transcription. This training began in the laboratory of my Ph.D. mentor, Lynne Maquat, where I studied the genetic and biochemical requirements for expression of glycolytic enzymes linked to metabolic disease. As a postdoctoral fellow in the laboratory of Arnold Berk, I refined my expertise in the biochemistry and genetics of the core Pol II apparatus. This work led to my seminal discovery of human Mediator, a conserved multisubunit signal-processor through which regulatory information conveyed by gene-specific transcription factors is transduced to Pol II. As an independent investigator, I have leveraged my basic knowledge in the biochemistry of Mediator to investigate how its dysfunction elicits developmental disease and tumorigenesis. In this regard, we discovered that somatic mutations in Mediator subunit 12 (MED12) responsible for ~80% of uterine fibroids disrupt Mediator-associated CDK8 activity leading to aberrant RNA polymerase II function genome-wide. The studies proposed herein aim to extend these novel findings and elucidate the molecular basis and therapeutic implications of Mediator kinase disruption in the pathogenesis of MED12-mutant fibroids. In addition to the intellectual and technical resources that my own research team brings to bear on this problem, I have recruited a world-class team of skilled collaborators who offer leading expertise in genetics, clinical pathology, and translational models of uterine fibroids, rendering us ideally positioned to successfully complete our study aims.

1. Turunen, M., Spaeth, J.M., Keskitalo, S., Park, M.J., Kivioja, T., Clark, A.D.,... H., Vahteristo, P., Kim, C.A., Aaltonen, L.A., Varjosalo, M., Taipale, J., and Boyer, T.G. (2014) Uterine-leiomyoma-linked MED12 mutations disrupt Mediator-associated CDK activity. **Cell Rep** 7: 654-660. PMCID: PMC4041330  
**\*Featured Highlight:** Alderton, G.K. (2014) Transcription: Mediating tumorigenesis. **Nat Rev Cancer** 14: 382. PMID: 24854073
2. Kampjarvi, K., Park, M.J., Mehine, M., Kim, N.H., Clark, A.D.,...van de Spuy, Z.M., Sjoberg, J., Boyer, T.G., and Vahteristo, P. (2014) Mutations in exon 1 highlight the role of MED12 in uterine leiomyomas. **Hum Mut** 35: 1136-1141. PMID: 24980722
3. Kampjarvi, K., Kim, N.H., Keskitalo, S., Clark, A.D., von Nandelstadh, P., Taipale, J., Varjosalo, M., Boyer, T.G., and Vahteristo, P. (2016) Somatic MED12 mutations in prostate cancer and uterine leiomyomas promote tumorigenesis through distinct mechanisms. **Prostate** 76: 22-31. PMID: 26383637
4. Al-Hendy, A., Diamond, M.P., Boyer, T.G., and Halder, S.K. (2016) Vitamin D3 inhibits Wnt/ $\beta$ -catenin and mTOR signaling pathways in human uterine fibroid cells. **J Clin Endocrinol Metab** 101: 1542-1551. PMID: 26820714
5. Al-Hendy, A., Laknauer, A., Diamond, M.P., Ismail, N., Boyer, T.G., and Halder, S.K. (2016) Silencing Med12 gene reduces proliferation of human leiomyoma cells mediated via Wnt/ $\beta$ -catenin signaling pathway. **Endocrinology** Dec 14:en20161097 [Epub ahead of print]. PMID: 27967206

## B. POSITIONS AND HONORS

### Professional Experience:

1983-1985	<b>Research Associate</b> , Biotech Research Laboratories, Rockville, MD
1985-1991	<b>Graduate Research Assistant</b> , Department of Biochemistry, SUNY at Buffalo Mentor: Dr. Lynne E. Maquat
1991-1998	<b>Postdoctoral Fellow</b> , Department of Microbiology and Molecular Genetics, UCLA Mentor: Dr. Arnold J. Berk
1999-2006	<b>Assistant Professor</b> , Department of Molecular Medicine University of Texas Health Science Center at San Antonio
2001-2005	<b>Director</b> , Institute of Biotechnology MALDI Mass Spectrometry Core University of Texas Health Science Center at San Antonio
2005-2010	<b>Associate Professor</b> , Department of Molecular Medicine University of Texas Health Science Center at San Antonio
2010-Present	<b>Professor</b> , Department of Molecular Medicine University of Texas Health Science Center at San Antonio

### Professional Service:

2005-06	USAMRMC/DOD BCRP IDEA, Endocrinology Panel Review Member
2006	USAMRMC/DOD BCRP CONCEPT, Endocrinology Panel Review Member
2008	NIH Molecular Oncogenesis Study Section, Ad Hoc Member
2009	NIH Cancer Etiology Study Section, Ad Hoc Member
2009-Present	International Journal of Biological Sciences, Editorial Board Member
2010	NIH Cancer Molecular Pathology Study Section, Ad Hoc Member
2011	NIH Molecular Genetics A Study Section, Ad Hoc Member
2016	NIH ZCA1 RPRB-C(J1) R Emerging Questions in Cancer Systems Biology (U01)

### Honors and Awards

1983	Magna Cum Laude and Departmental Honors in Biology; Frostburg State University
1990-1991	California Institute for Cancer Research Fellowship
1991-1994	American Cancer Society Fellowship
1995-1998	American Cancer Society Fellowship
1999	Parvin Postdoctoral Recognition Award, UCLA
2002-2007	Career Development Award, U.S. Army DOD Breast Cancer Research Program
2002-2003	U.S. Army DOD BCRP Research Recognition Award, Alamo Breast Cancer Foundation
2002, '03, '13	Executive Research Committee Merit Award, UTHSCSA

## C. CONTRIBUTION TO SCIENCE

### 1. BRCA1: Molecular basis for its breast tumor suppressor function

Our early studies aimed to understand how germline inactivation of the BReast CAncer susceptibility gene, *BRCA1*, confers a cumulative lifetime risk of breast (and ovarian) cancer. Our work contributed significantly to the current concept of *BRCA1* as a cellular caretaker that ensures global genome stability by coupling DNA damage-induced signals to downstream responses, including DNA damage repair and cell cycle checkpoint activation. In this regard, we identified a novel role for *BRCA1* as a sequence-specific transcriptional co-repressor of DNA damage-response genes and further linked disruption of this important function to its inherent tumor suppressor properties. We also identified a novel function for *BRCA1* in direct repair of damaged DNA through a homologous recombination-independent pathway (non-homologous end-joining). Notably, our work further clarified the molecular basis for the tissue-specific tumor suppressor function of *BRCA1*, which cannot be adequately explained by its universal role as a genomic caretaker. Thus, we showed that *BRCA1* suppresses estrogen signaling, and further linked this activity with its biological function as a breast and ovarian-specific tumor suppressor. Taken together, our early studies helped shape current paradigmatic views of *BRCA1* as a ubiquitous genomic caretaker and tissue-restricted breast- and ovarian-specific tumor suppressor.

1. Zheng, L., Pan, H., Li, S., Fleskin-Nitkin, A., Chen, P.L., Boyer, T.G., and Lee, W.H. (2000) Sequence-specific transcriptional corepressor function for *BRCA1* through a novel zinc finger protein, ZBRK1. *Mol Cell* 6: 757-768. PMID: 11090615

**\*Featured Previewed Article:** MacLachlan, T.K. and El-Deiry W.S. (2000) Pointing (zinc) fingers at *BRCA1* targets. *Nat Med.* 6: 1318-1319. PMID: 11100109

2. Zheng, L., Annab, L.A., Afshari, C.A., Lee, W.H., and Boyer, T.G. (2001) BRCA1 mediates ligand-independent transcriptional repression of the estrogen receptor. **Proc Natl Acad Sci, USA** 98: 9587-9592. PMID: PMC55496  
**\*Special Featured Article:** Reynolds, T. (2001) BRCA1: lessons learned from the breast cancer gene. **J Natl Cancer Inst** 93: 1200-1202. PMID: 11504763
3. Lee, W.H. and Boyer, T.G. (2003) BRCA1 and BRCA2 in breast cancer. *Lancet* 358:S5. PMID: 11784554.
4. Trauernicht, A.M. and Boyer, T.G. (2003) BRCA1 and estrogen signaling in breast cancer. **Breast Dis** 18: 11-20. PMID: 15687685
5. Lu, M., Chen, D., Lin, Z., Reierstad, S., Trauernicht, A.M., Boyer, T.G., and Bulun, S.E. (2006) BRCA1 negatively regulates the cancer-associated aromatase promoters I.3 and II in breast adipose fibroblasts and malignant epithelial cells. **J Clin Endocrinol Metab** 91: 4514-4519. PMID 16940443

## 2. Human Mediator: An integrative hub for signal-dependent gene regulation

A central outstanding question in metazoan biology concerns the means by which developmental, environmental, or homeostatic signals are effectively coupled with precise gene expression output sufficient to specify cell fate and function. While the underlying mechanisms have not yet been completely elucidated, this process nonetheless depends to a large extent on intermediary activities that link signal-regulated and chromatin-bound transcription factors with the core RNA Polymerase II (Pol II) transcription machinery. Central among these so-called “co-regulators” is the multi-protein Mediator, originally discovered in the budding yeast *Saccharomyces cerevisiae*, and since found to be broadly conserved among eukaryotes. We were among the first to biochemically isolate and functionally characterize human Mediator, the first to implicate Mediator in metazoan development, and the first to ascribe a function for Mediator as an endpoint in signal transduction pathways. Our work has fundamentally advanced the concept of Mediator as an integrative hub through which regulatory information conveyed by signal-regulated transcription factors is transduced to Pol II. Furthermore, we have contributed significantly to the notion of Mediator as a sensor, integrator, and processor of developmental and oncogenic signals that converge on protein-coding gene promoters, with profound implications for development and disease.

1. Boyer, T.G., Martin, M.E.D., Lees, E., Ricciardi, R.P., and Berk, A.J. (1999) Mammalian Srb/Mediator complex is targeted by adenovirus E1A protein. **Nature** 399: 276-279. PMID: 10353252  
**\*Featured Previewed Article:** Kingston, R.E. (1999) A shared but complex bridge. **Nature** 399: 199-200.
2. Kim, S., Xu, X., Hecht, A., and Boyer, T.G. (2006) Mediator is a transducer of Wnt/ $\beta$ -catenin signaling. **J Biol Chem** 281: 14066-14075. PMID: 16565090
3. Zhou, H., Kim, S., Ishii, S., and Boyer, T.G. (2006) Mediator modulates Gli3-dependent Sonic hedgehog signaling. **Mol Cell Biol** 26: 8667-8682. PMID: PMC1636813
4. Xu, X., Zhou, H., and Boyer T.G. (2011) Mediator is a transducer of amyloid-precursor-protein-dependent nuclear signaling. **EMBO Rep** 12: 216-222. PMID: PMC3059912  
**\*Featured Previewed Article:** Turner, A.J. et al. (2011) Mediator: the missing link in amyloid precursor protein signaling **EMBO Rep** 12: 180-181. PMID: PMC3059916
5. Kim, N.H., Livi, C. B., Yew, P.R., and Boyer, T.G. (2016) Mediator subunit MED12 contributes to the maintenance of neural stem cell identity. **BMC Dev Biol** 16(1): 16: 7. PMID: 27188461

## 3. Mediator and human disease

My laboratory has been at the forefront of efforts to understand how altered signaling as a consequence of genetic variation in Mediator triggers developmental disorders, neurodegenerative disease, and cancer. For example, landmark studies from my laboratory revealed that mutations in Mediator responsible for syndromic forms of X-linked intellectual disability disrupt proper epigenetic controls over neuronal gene expression and normal constraints on Sonic hedgehog signaling. More recently, we elucidated the functional impact and continue to investigate the molecular bases by which Mediator mutations drive the formation of multiple cancer types, including colorectal, prostate, and blood cancers. Together, these studies highlight the component nature and pathogenic vulnerability of Mediator and suggest new therapeutic strategies with possible applications across a range of human pathologies.



## **MOLECULAR PATHOGENESIS AND EPIGENOMIC LANDSCAPE OF UTERINE LEIOMYOMAS**

Uterine leiomyomas (LM; or fibroids) are monoclonal neoplasms of the myometrium (MM) and represent the most common tumors in women worldwide. Although benign, they nonetheless account for significant gynecologic and reproductive dysfunction, ranging from profuse menstrual bleeding and pelvic pain to infertility, recurrent miscarriage, and pre-term labor. As no long-term non-invasive treatment option currently exists for LM, deeper insight concerning tumor etiology is key to the development of newer targeted therapies. Accordingly, this project is impactful as it suggests an etiologic basis for the predominant LM subtype and further offers proof of concept for therapeutic intervention in this specific genetic setting.

LM arise from the genetic transformation of a single MM stem cell (SC) into a tumor-initiating cell (LM SC) that seeds and sustains fibroid growth through asymmetric cell divisions and monoclonal expansion. Heretofore, the genetic drivers thought dominantly responsible for fibroid formation have been largely identified. The most prevalent among these, accounting for ~80% of LM, are recurrent somatic mutations in the gene encoding the MED12 subunit of Mediator, a conserved multiprotein signal processor through which regulatory information conveyed by gene-specific transcription factors is transduced to RNA polymerase II (Pol II). However, the impact of these mutations on MED12 function and the molecular basis for their tumorigenic potential are unknown. Recently, we found that LM-linked mutations in MED12 disrupt its ability to activate Cyclin C (CycC)-dependent kinase 8 (CDK8) in Mediator, leading to reduced site-specific RNA Pol II phosphorylation and global dysregulation of gene expression. Furthermore, we identified genetic programs uniquely dysregulated in MED12-mutant fibroids, leading us to hypothesize that Mediator kinase disruption as a consequence of MED12 mutations elicits transcriptional reprogramming and altered signaling sufficient to drive MM SC transformation. We further hypothesize that MED12-mutant LM are therapeutically susceptible to reactivation of CDK8 or pharmacologic modulation of uniquely dysregulated downstream signaling pathways. To confirm and extend these hypotheses, we are engaged in the followed studies, which we expect to significantly impact personalized treatment of women with LM.

### **Establish the pathogenic role of Mediator kinase disruption in MED12-mutant LM.**

Our discovery that LM-linked MED12 mutations disrupt CDK8 activity in Mediator implies a new etiological role for CDK8 dysfunction as an important driver of uterine fibroids. To test this prediction, we will ask if genetic or chemical disruption of CDK8 (or its paralog CDK19) is sufficient to induce MM SCs to undergo fibrotic transformation in vitro and form fibroid tumors in vivo. The deleterious impact of mutations in MED12 on its CDK8-stimulatory activity marks them as loss of function mutations and thus reveals MED12 to be a probable tumor suppressor in MM. To test this prediction, we will ask if WT MED12, through restoration of CDK8/19 activity, can suppress the fibrotic phenotype of MED12-mutant LM SCs both in vitro and in vivo.

### **Elucidate the pathogenic mechanism of Mediator kinase disruption in MED12-mutant LM.**

The molecular basis by which mutant MED12 disrupts CDK8/19 activity leading to tumorigenesis is unknown. To address the biochemical impact of mutant MED12, we will deploy a combination of in vitro binding and enzyme kinetic analyses to determine whether and how MED12 alters the catalytic efficiency of CycC-CDK8/19, define the role of MED12 in the overall activation mechanism, and clarify how pathogenic mutations in MED12 disrupt this process. To address the molecular basis by which Mediator kinase disruption drives MED12-mutant fibroid formation, we will employ an integrated genome-scale approach. Using RNA- and ChIP-seq in autologous MM and LM SCs, we will acquire tumor- and mutation-specific transcriptomic and epigenomic profiles. This combined analysis will permit us to correlate pathologic changes in gene expression with alterations in Pol II phosphorylation dynamics and super-enhancer activity, providing unprecedented insight into the basis by which MED12 mutations alter transcriptional programs as a course of tumorigenesis.

### **Examine the therapeutic implications of Mediator kinase disruption in MED12-mutant LM.**

We hypothesize that transcriptional reprogramming, as a pathological consequence of Mediator kinase disruption, is also a pathogenic trigger of fibrotic transformation. If true, this leads to several predictions with implicit therapeutic considerations. First, reactivation of CDK8/19 in MED12-mutant LM may prove anti-tumorigenic. To test this, we will ask if pharmacologic restoration of CDK8/19 with peptide activators can transcriptionally program MED12-mutant LM SCs and suppress their fibrotic phenotype. Second, targeted modulation of signaling pathways uniquely dysregulated in MED12-mutant tumors, including the Wnt/ $\beta$ -catenin and glucocorticoid receptor (GR) pathways, may alternatively prove therapeutic. To test this, we will ask whether chemical modulation of these pathways can suppress the fibrotic phenotype of MED12-mutant LM SCs. These studies are the first to implicate GR signaling in the pathobiology of LM, and we will exploit these novel insights to establish proof-of-concept for the use of CDK8 activators and GR agonists in LM therapy.